EXHIBIT A

JP-A-56-131394

Specification

1. Title of the Invention

Method for purifying coenzyme Q

2. Claim

A method for purifying coenzyme Q, comprising putting a solution of crude coenzyme Q in a hydrophobic solvent in contact with an aqueous ammonia-alcohol solution to transfer impurities contained in the crude coenzyme Q to the aqueous ammonia-methanol solution, to remove the impurities from the crude coenzyme Q.

3. Detailed Description of the Invention

The present invention relates to a method for purifying coenzyme Q. More specifically, the invention relates to a method for purifying coenzyme Q, using an aqueous ammonia-methanol solution.

Coenzyme Q is involved in the electron transport system in biological organisms. Coenzyme Q exerts excellent pharmacological effects on various diseases such as cardiac function impairment, myasthenia gravis and emphysema. The coenzyme Q can be obtained synthetically or via extraction from microbial cells or naturally occurring materials. The coenzyme Q obtained by these methods contains a lot of impurities therein, so that the coenzyme

Q is at a very low purity. Therefore, such coenzyme Q is necessarily purified so as to apply the resulting coenzyme Q to practical uses such as medicine.

Various methods exist for purifying coenzyme Q, including for example purification by chromatography on silica gel columns and by crystallization using solvents such as acetone, methanol and methyl ethyl ketone. Nonetheless, these methods have various disadvantages for purifying the coenzyme Q containing a great number of impurities, as it is. These methods are frequently disadvantageous industrially.

Because purification by chromatography on silica gel columns requires precise fractionations, specifically, such purification demands laborious procedures and loads extremely serious burdens to such columns, so that it is hard to treat such coenzyme Q at a mass scale. By crystallization, frequently, the crystal is hardly deposited or absolutely no such crystal is deposited.

Further, preferably, impurities should be removed as much as possible by purification. However, then, the intended substance is generally lost at a large scale, disadvantageously.

The present inventors made investigations so as to industrially advantageously carry out such purification methods of coenzyme Q as described above to remove impurities

as much as possible and reduce the loss of coenzyme Q as much as possible. Thus, the invention has been achieved.

Specifically, the invention relates to a method for purifying coenzyme Q, comprising putting a solution of crude coenzyme Q in a hydrophobic solvent in contact with an aqueous ammonia-alcohol solution to transfer impurities contained in the crude coenzyme Q to the aqueous ammonia-methanol solution, to remove the impurities from the crude coenzyme Q.

The term crude coenzyme Q in accordance with the invention means crude coenzyme Q containing impurities together with coenzyme Q_{4-12}. Specifically, the crude coenzyme Q includes for example crude coenzyme Q extracted from biological organisms such as microbial cells, animal organs and fish meat with a bloody color, or crude coenzyme Q concentrated in a solution resulting from a reaction for synthetically preparing coenzyme Q, and additionally includes concentrated crude coenzyme Q after purification.

Methods for extracting coenzyme Q from biological organisms such as microbial cells, animal organs and fish meat with a bloody color include general methods for example an extraction method at ambient temperature or at a state under heating, using solvents such as pyridine, methanol, ethanol, ethyl ether, acetone or acetonitrile, a method comprising saponification with an alcoholic alkali in the

presence of pyrogallol and subsequent extraction, a method comprising a treatment with acids and alkalis and a subsequent liquid/liquid extraction from an aqueous suspension of a substance containing coenzyme Q, using aqueous solvents. Furthermore, the coenzyme Q prepared by extraction in such manner or prepared synthetically is preliminarily treated for removing a part of impurities, by extraction in n-hexane, acetone or acetonitrile, rinsing in methanol and crystallization using acetone, ethanol or methyl ethyl ketone. Then, the resulting product is defined as the crude coenzyme in accordance with the invention, with no problem.

The content ratio of water and volatile substances such as solvents in the crude coenzyme Q to be purified in accordance with the invention is preferably as low as possible.

The hydrophobic solvent for dissolving the crude coenzyme Q for use in accordance with the invention includes any solvent compounds, satisfactorily, as long as the compounds can dissolve coenzyme Q but are never compatible with the aqueous ammonia-methanol solution. As the hydrophobic solvent, for example, aliphatic hydrocarbons such as n-hexane, n-pentane, n-heptane and isooctane, alicyclic hydrocarbons such as cyclohexane, and aromatic hydrocarbons such as benzene, toluene and xylene, and

mixtures of these hydrocarbons, and petroleum ether are preferably used in a practical sense.

The hydrophobic solvent is used at an amount to dissolve the coenzyme Q in the crude coenzyme Q. Practically, the hydrophobic solvent is generally used at a ratio of about 0.2 to 20 ml per 1 g of crude coenzyme Q. Herein, insoluble matters may sometimes precipitate or float in the hydrophobic solvent solution of crude coenzyme Q. The insoluble matters may satisfactorily be removed, if necessary.

As the hydrophobic solvent solution of crude coenzyme Q, additionally, a solution of crude coenzyme Q preliminarily prepared as described above in a hydrophobic solution may be used. Still additionally, an extract solution of crude coenzyme Q as prepared by using a hydrophobic solvent for extraction or purification as an extraction agent may be used as it is.

The aqueous ammonia-alcohol solution in accordance with the invention is a mixture solution of aqueous ammonia and an alcohol. The ammonia concentration in the aqueous ammonia is not specifically limited. However, practically, the ammonia concentration is preferably 10 to 30 wt %. Generally, lower aliphatic alcohols such as methanol and ethanol are used as the alcohol. Particularly, methanol is the most preferable. The content ratio of the aqueous

ammonia in the aqueous ammonia-alcohol solution is not specifically limited. Practically, the content ratio is preferably 2 to 40 vol %.

The volume of the aqueous ammonia-alcohol solution to be put in contact with the hydrophobic solvent solution of crude coenzyme Q is not specifically limited. Practically, the volume thereof is preferably about 1/20-fold to 1-fold the volume of the hydrophobic solvent solution of the crude coenzyme.

The hydrophobic solvent solution of the crude coenzyme Q is put in contact with the aqueous ammonia-alcohol solution, for example by mixing together the two solutions and agitating the resulting mixture at ordinary temperature to ambient temperature for about 5 minutes or more, practically preferably for about 5 minutes to 2 to 3 hours. Subsequently, the resulting solution is left to stand alone to separate a layer of light weight solutions and a layer of heavy weight solutions. Then, the layer of light weight solutions is taken out. The layer of light weight solutions corresponds to the hydrophobic solvent solution of coenzyme Q, from which impurities are preliminarily removed. The layer of heavy weight solutions corresponds to the aqueous ammonia-alcohol solution containing impurities.

The contact is done once satisfactorily. However, the contact may be done twice to five times, in a repeated

manner.

Insoluble matters may sometimes float in the layer of light weight solutions, so such insoluble matters should be removed.

Additionally, a trace amount of ammonia is in dissolution in the layer of light weight solutions. The ammonia is preferably removed. The means for removing ammonia includes for example the evaporation of ammonia under reduced pressure in a short time or putting the layer of light weight solutions in contact with aqueous alcohol solutions.

For the latter, the alcohol includes lower aliphatic alcohols such as methanol and ethanol. Particularly, methanol is preferable. The alcohol concentration in the aqueous alcohol solution is practically about 60 vol %, or more preferably 60 to 98 vol %, particularly preferably 80 to 98 vol %. Regarding the conditions for the contact, for example, the aqueous alcohol solution is used at a volume 1/20-fold to 1-fold the volume of the layer of light weight solutions, preferably, for agitation at ordinary temperature to ambient temperature for 2 to 3 hours. The contact may be done once or may be repeated twice to five times, satisfactorily.

By removing the hydrophobic solvent from the resulting layer of light weight solutions obtained in such manner, for

example by concentration under reduced pressure, coenzyme Q is obtained.

By the method of the invention, about 20 to 90 wt % of impurities contained in crude coenzyme Q can be removed.

So as to raise the purity of the coenzyme Q thus obtained, it is required to repeatedly carry out additional purification. For the purification, there can be listed purification by column chromatography and purification via crystallization using solvents such as acetone, ethanol or methyl ethyl ketone under cooling to -20 to 5°C. In case that coenzyme Q is contaminated with impurities at the same amount as that of coenzyme Q or more, the impurities are preferably removed preliminarily by column chromatography for the crystallization. When recrystallization is repeatedly carried out following the crystallization, coenzyme Q at an extremely high purity can be obtained.

According to the method of the invention, coenzyme Q at a high purity can be obtained readily at a high yield by an extremely simple treatment. Furthermore, the method can treat a large amount readily. The method also reduces continuous, laborious purification procedures. Furthermore, the method reduces difficulty involved therein, so the method can be done industrially advantageously.

The method is specifically described in the following Examples. However, the method is never limited to the

Examples described below.

Example 1

0.5 kg of $(NH_4)_2SO_4$, 0.75 kg of $MgSO_4 \cdot 7H_2O$, 2.25 kg of KH_2PO_4, 15 g of $FeC_6H_5O_7 \cdot xH_2O$, 45 g of $CaCl_2 \cdot 2H_2O$, 7.5 g of $ZnSO_4 \cdot 7H_2O$, 7.5 g of $MnCl_2 \cdot 4H_2O$, 0.75 g of $CuSO_4 \cdot 5H_2O$, 0.5 g of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, 0.5 g of $CoCl_2 \cdot 2H_2O$, 0.5 g of H_3BO_3, 25 g of NaCl and 0.5 g of KI were dissolved in 500 liters of industrial water; the resulting solution was adjusted to pH 7.0 and then sterilized, to which 7 kg of methanol was added. In the resulting mixture was inoculated *Protaminobacter ruber NCIB 2879* precultured for 3 days in 30 liters of a culture medium of a similar composition containing methanol at 1 wt %, for culturing under aeration at 500 l/min at 28°C and agitation at 1000 rpm for 3 days. The liquid culture was retained at pH 7.0, by adding aqueous ammonia to the liquid culture. After culturing, the bacteria were collected with a centrifuge machine and dried with a spray dryer, to obtain dry bacterial cells at 1.8 kg. To 1.8 kg of the dry bacterial cells was added acetone of 6 liters, for agitation at 30°C for one hour for extraction. Subsequently, the bacterial cells are filtered off. The procedure was repeatedly carried out three times. Extract solutions resulting from the extractions three times were combined together, from which the solvents were removed by

concentration under reduced pressure, to obtain 10 g of crude coenzyme Q_{10}(I).

10 g of the crude coenzyme Q_{10}(I) was dissolved in 100 ml of n-hexane, from which insoluble matters were filtered off. 20 ml of an aqueous ammonia-methanol solution at a 5-vol % content of aqueous ammonia at a 28-wt % ammonia concentration was added to the solution, for agitation at 10°C for 20 minutes. Subsequently, the resulting solution was left to stand alone, to separate the n-hexane layer and the aqueous ammonia-methanol solution layer. The aqueous ammonia-methanol solution layer was then removed. The procedure was repeatedly carried out twice. 20 ml of an aqueous methanol solution at a 95-vol % methanol concentration was added to the n-hexane layer thus obtained, for agitation at 10°C for 20 minutes. Then, the resulting solution was left to stand alone, to separate the n-hexane layer and the aqueous methanol solution layer, which was then removed. The n-hexane layer was concentrated under reduced pressure to remove the solvent therein, to obtain crude coenzyme Q_{10}(II) at 3.0 g. About 85 % of the impurities in the crude coenzyme Q_{10}(I) was removed.

3.0 g of the crude coenzyme Q_{10}(II) was dissolved in 30 ml of acetone. The resulting solution was left to stand alone in a deep freezer at -10°C for 2 hours. After it was confirmed that the solution was at 5°C or lower, 0.1 mg of

the powder of coenzyme Q_{10} at a purity of 99.8 % was added to the solution. The resulting solution was left to stand alone for two days and two nights in a freezer, from which the deposited crystal was recovered by filtration. The crystal was dried in vacuum at ambient temperature in a state under protection from light for all day and night, to obtain the crystal of coenzyme Q_{10} at 2.2 g. The purity thereof was 82 %.

Alternatively, 10 g of crude coenzyme Q_{10}(I) obtained by the same method as described above was subjected as such to crystallization procedures in the same manner as described above. However, no crystal was deposited.

Example 2

0.5 kg of $(NH_4)_2SO_4$, 0.75 kg of $MgSO_4 \cdot 7H_2O$, 2.25 kg of KH_2PO_4, 15 g of $FeC_6H_5O_7 \cdot xH_2O$, 45 g of $CaCl_2 \cdot 2H_2O$, 7.5 g of $ZnSO_4 \cdot 7H_2O$, 7.5 g of $MnCl_2 \cdot 4H_2O$, 0.75 g of $CuSO_4 \cdot 5H_2O$, 0.5 g of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, 0.5 g of $CoCl_2 \cdot 2H_2O$, 0.5 g of H_3BO_3, 25 g of NaCl and 0.5 g of KI were dissolved in 500 liters of industrial water; the resulting solution was adjusted to pH 4.0 and then sterilized, to which 7 kg of methanol was added. In the resulting mixture was inoculated *Pichia pastoris IFO-1013* precultured for 3 days in 30 liters of a culture medium of a similar composition containing methanol at 1 wt %, for culturing under aeration at 500 l/min

at 30°C and agitation at 1000 rpm for 3 days. The liquid culture was retained at pH 4.0, by adding aqueous ammonia to the liquid culture. After culturing, the bacteria were collected with a centrifuge machine, to obtain 10 kg of wet bacterial cells (dry bacterial cells at an amount of 1.8 kg). The bacterial cells were suspended in 19 liters of methanol, to which 4700 ml of 60 wt % caustic soda and 950 g of pyrogallol were added for saponification. To the resulting saponified solution was added water of 70 liters. n-Pentane of a volume equal to the volume of the resulting solution was used for extraction three times. The resulting n-pentane layer was rinsed in water, dehydrated and concentrated, to obtain crude enzyme $Q_8(I)$.

6 g of the coenzyme $Q_8(I)$ was dissolved in 100 ml of n-pentane, to which 20 ml of an aqueous ammonia-methanol solution at a 20-vol % content of aqueous ammonia at an ammonia concentration of 14 wt % was added, for agitation at 20°C for 30 minutes. Then, the resulting solution was left to stand alone, to separate the n-pentane layer and the aqueous ammonia-methanol solution layer. The aqueous ammonia-methanol solution layer was removed. After the procedure was repeatedly carried out twice, 20 ml of an aqueous methanol solution at a methanol concentration of 95 vol % was added to the n-pentane layer, for agitation at 20°C for 30 minutes. The resulting solution was left to stand

alone, to separate the n-pentane layer and the aqueous methanol solution layer. The aqueous methanol solution layer was removed. The n-pentane layer was concentrated under reduced pressure to remove the solvent therein, to obtain crude coenzyme Q_8(II) of 2.0 g. About 80 % of impurities in the crude coenzyme Q_8(I) was removed.

2.0 g of the crude coenzyme Q_8(II) was dissolved in 20 ml of methyl ethyl ketone and then left to stand alone in a deep freezer at -10°C for 2 hours. After it was confirmed that the solution was at 5°C or lower, 0.1 mg of the powder of coenzyme Q_8 at a purity of 99.8 % was added. After the resulting mixture was left to stand alone in a freezer for two days and two nights, the deposited crystal was recovered by filtration. The crystal was dried in vacuum at ambient temperature at a state under protection from light for all day and night, to obtain the crystal of coenzyme Q_8 at 1.3 g. The purity thereof was about 77 %.

Alternatively, 6 g of crude coenzyme Q_8(I) obtained by the same method as described above was subjected as such to crystallization procedures in the same manner as described above. However, no crystal was deposited.

Example 3

5 g of crude coenzyme Q_{10}(III) obtained by a reaction between isodecaprenol and

2,3-dimethoxy-5-methylhydroquinone was dissolved in 50 ml of cyclohexane. To the resulting solution was added 10 ml of an aqueous ammonia-methanol solution at a 3-vol % content of 30 wt % aqueous ammonia, for agitation at 30°C for 15 minutes. The resulting solution was left to stand alone, to separate the cyclohexane layer and the aqueous ammonia-methanol solution layer. The aqueous ammonia-methanol solution layer was removed. After the procedure was repeatedly carried out twice, 10 ml of an aqueous methanol solution at a methanol concentration of 97 vol % was added to the cyclohexane layer, for agitation at 30°C for 15 minutes. The resulting solution was left to stand alone, to separate the cyclohexane layer and the aqueous methanol solution layer. The aqueous methanol solution layer was removed. The cyclohexane layer was concentrated under reduced pressure to remove the solvent therein, to obtain crude coenzyme Q_{10}(IV) at 3.0 g. About 64 % of impurities in the crude coenzyme Q_{10}(III) was removed. 3 g of the crude coenzyme Q_{10}(IV) was dissolved in 15 ml of acetone, to which 15 ml of methanol was added. The resulting solution was left to stand alone in a deep freezer at -10°C for 2 hours. After it was confirmed that the solution was at 5°C or lower, 0.1 mg of the powder of coenzyme Q_{10} at a purity of 99.8 % was added. Further, the resulting mixture was left to stand alone in a freezer for two days and two

nights. The resulting deposited crystal was recovered by filtration. The crystal was dried in vacuum at ambient temperature in a state under protection from light for all day and night, to obtain the crystal of coenzyme Q_{10} at 2.5 g. The purity thereof was about 75 %.

Alternatively, 5 g of crude coenzyme Q_{10}(III) obtained by the same method as described above was subjected as such to crystallization procedures in the same manner as described above. However, no crystal was deposited.

EXHIBIT B

solation Liquefaction of a gel; the reverse of gelation.

solbrol Nipagin M.

solder Braze. A fusing metal or alloy used to unite adjacent surfaces of less fusible metals. **brass ~** Copper s. **copper ~** An alloy: Sn 5, Pb 2 pts., with zinc chloride as flux. **fine ~** Soft s. **fusible ~** An alloy of Pb, Sn, and Bi, which melts in water; used in spray fire extinguishers. **gold ~** An alloy: Au 10, Ag 6, Cu 4 pts. **hard ~** A high-melting-point alloy used as s.; it fuses at red heat: e.g., Cu + Zn + Ag. **lead ~** An alloy of equal parts of Pb and Sn, used for soldering lead. **plumber's ~** An alloy usually containing approx. Pb 65, Sn 30%, with some Sb. **seifert ~** A s. for aluminum, containing Sn 73, Zn 21, Pb 5%. **silver ~** See *silver solder*. **soft ~** A s. that fuses below red heat; as, Sn + Pb; *lead* s. (above), *fusible* s. **zinc ~** An alloy: Sn 5, Pb 3 pts.

soldering (1) Uniting metallic pieces by heat with or without an alloy (solder) and flux (borax). (2) In commerce, soft (as distinct from hard) solders. S. differs from *brazing* and fusion *welding*, q.v. **autogenous ~** Uniting metal surfaces by interfusion, without a more fusible alloy. **fusing ~** Uniting metal surfaces by filling all intervening space with a completely fused solder. **sweating ~** S. in which the solder is heated near its melting point and adheres.

solenhofen stone A fine-grained, porous limestone; contains clay.

solenoid A hollow cylinder, wound with resistance wire; used to produce fields of electric force, as to operate a valve.

solfatara A volcanic vent from which sulfur is obtained.

solferino Fuchsin.

solid (1) A substance of definite shape, and relatively great density, low internal enthalpy, and great cohesion of its molecules. It may be homogeneous (as crystals and solid solutions) or hetergeneous (as amorphous and colloidal substances). **s. solution** (1) Sosoloid. A homogeneous, s. mixture of a substance; as, glass. (2) A s. solution of a solid, liquid, or gas in a solid. **s. state** Describing electronic components that utilize electronic and magnetic properties of solids.

solidago Goldenrod. The dried herb of *Solidago odora* (Compositae); a carminative.

solidify To change into the solid state.

solidifying point Freezing point.

solidus In a temperature-concentration diagram for both solid and liquid solutions whose concentrations differ, the s. curve relates to the solid phase, and the *liquidus* to the liquid phase.

soliquoid Suspension. A dispersed system of a solid phase in a liquid phase.

soln. Abbreviation for solution.

solodization Dealkalization. Removal of alkali from soils by degradation.

Solozone Trademark for a brand of hydrogen peroxide.

solubility The extent to which a substance (solute) mixes with a liquid (solvent) to produce a homogeneous system (solution). The classification used by the United States Pharmacopeia is shown in Table 85. **apparent ~** The total amount of undissociated and dissociated portions of a substance dissolved in a liquid. **degree of ~** The concentration of a saturated solution at a given temperature. S. generally increases with increase in temperature. **molar ~** c/M, where c is the g/L and M the molecular weight. **real ~** The amount of undissociated solute in a liquid. **s. curve** A graph obtained by plotting the amount of dissolved substance in a saturated solution against the temperature. **s. exponent** p or p_s = log 1/S. Cf. *pH*. **s. product** $S = [M^+] \times [X^-]/[MX]$, where the brackets indicate the concentrations of the components of the dissociation equilibrium: $MX \rightleftharpoons M^+ + X^-$. If $[M^+] \times [X^-]$ exceeds S, MX will precipitate; and vice versa. E.g., NaCl is precipitated from concentrated solutions by HCl gas.

TABLE 85. USP SOLUBILITY CLASSIFICATION

Description	Parts of solvent required for 1 part of solute
Very soluble	Less than 1
Freely soluble	1–10
Soluble	10–30
Sparingly soluble	30–100
Slightly soluble	100–1,000
Very slightly soluble	1,000–10,000
Practically insoluble or insoluble	10,000+

soluble Capable of mixing with a liquid (dissolving) to form a homogeneous mixture (solution). Cf. *solubility, solution*. **s. barbital** Sodium *barbitone*. **s. cotton** Nitrocellulose. **s. glass** Sodium silicate. **s. mercury** $NH_2Hg_2NO_3 \approx 479.2$. Hahnemann's mercury. Black precipitate on adding ammonia to mercurous nitrate. **s. starch** See *starch soluble*. **s. tartar** Ammonium potassium tartrate*. **s. tartrate** Potassium tartrate.

solum A damp-resisting layer of material installed on the ground under a floor, e.g., bitumen.

solute A substance that mixes with or dissolves in a solvent to produce a solution.

solution (1) Dissolution. The mixing of a solid, liquid, or gaseous substance (solute) with a liquid (the solvent), forming a homogeneous mixture from which the dissolved substance can be recovered by physical processes. (2) The homogeneous mixture formed by the operation of s. **anisotonic ~** Any nonisotonic s.; as, a hypotonic or hypertonic s. **aqueous ~** A s. in which water is the main solvent. **buffer ~** A s. of acid or basic salts that can neutralize either acids or bases without appreciable change in hydrogen-ion concentration. **centinormal ~** A s. containing 0.01 equivalents per liter. **chemical ~** A s. in which solute and solvent react to form a compound that dissolves in the solvent and cannot be recovered by distillation. Cf. *physical solution*. **colloidal ~** A macroscopically homogeneous, microscopically heterogeneous, system of minute particles (colloid, dispersed phase) suspended in a liquid (continuous phase, medium). Cf. *colloid*. **concentrated ~** A s. in which the solute content is relatively great. **decinormal ~** A s. that contains 0.1 equivalents per liter. **dilute ~** A s. in which the solute is relatively small in quantity. **gram molecular ~** Molar s. **heat of ~** See *heat of solution*. **hypertonic ~** A s. whose osmotic pressure is greater than that of blood serum. **hypotonic ~** A s. whose osmotic pressure is less than that of blood serum. **ionic ~** A s. whose ions of the solute are surrounded by oriented molecules of the solvent. **isotonic ~** A s. having an osmotic pressure equal to that of blood serum; as, 0.9% w/v sodium chloride s. **molal ~** A s. containing 1 g molecule (mole) of substance per 1,000 g of s. **molar ~** A s. containing 1 g molecule of substance per liter. Cf. *normal solution*. **molecular ~** A true s. in which the molecules of solute are surrounded by molecules of solvent. Cf. *colloidal solution, ionic solution*. **normal ~** A s. containing 1 gram equivalent per liter. **normal salt ~** A s. containing 1 mole sodium chloride per liter. Cf. *isotonic*

EXHIBIT C

m.220, soluble in water. An antidote to organophosphorus insecticides (USP).

Prandtl number *Pr.* Specific heat capacity at constant pressure × kinematic viscosity/thermal conductivity. Cf. *Reynolds number.*

prase (1) Greenish. (2) A gray-green chalcedony.

praseodymia The earth corresponding with the element praseodymium.

praseodymium* Pr = 140.9077. A rare-earth metal, at. no. 59. Green metal, d.6.48, m.930, slowly decomp. in water. Separated (1885) by Auer von Welsbach from the earth didymia, and occurs in cerite and rare-earth minerals. Principal valency 3. See *didymium.* **p. acetate*** $Pr(C_2H_3O_2)_3 \cdot 3H_2O$ = 372.1. Green needles, soluble in water. **p. chloride*** $PrCl_3$ = 247.3. Green needles, m.818; soluble in water. **p. oxalate*** $Pr_2(C_2O_4)_3 \cdot 10H_2O$ = 736.1. Green crystals, insoluble in water. **p. oxides** (1)Pr_2O_3 = 329.8. P. trioxide*. Yellow-green powder. (2) Pr_2O_4 = 345.8. P. tetraoxide*. Black powder. (3)Pr_2O_5 = 361.8. P. pentaoxide*. **p. phosphate*** $PrPO_4$ = 235.9. Green powder for coloring ceramics. **p. sulfate*** $Pr_2(SO_4)_3 \cdot 8H_2O$ = 714.1. Green crystals, soluble in water. **p. sulfide*** Pr_2S_3 = 378.0. Brown powder, decomp. by heat, insoluble in water.

praseolite A green alteration product of iolite.

prazosin hydrochloride $C_{19}H_{21}O_4N_5 \cdot HCl$ = 419.9. Hypovase, Minipress. White crystals, 264 (decomp.). Used for hypertension and heart failure (USP).

preboarding The setting of hosiery fibers by the combined actions of steam and pressure.

Precambrian See *geologic eras,* Table 38 on p. 259.

precancerous Describing a growth which can or may develop into a cancer.

precious Valuable, rare. **p. garnet** Almandite. **p. metals** The noble metals: gold, platinum, and silver. **p. opal** An opal exhibiting a play of delicate colors. **p. stone** A mineral used as a gem.

precipitable Describing that which can be precipitated.

precipitant A substance which, when added to a solution, causes the formation of an insoluble substance. **group ~** A reagent that will precipitate several related substances; as, hydrogen sulfide or ammonia. See *qualitative analysis* under *analysis.*

precipitate Abbrev. ppt (no period). (1) To cause a substance to be precipitated. (2) The deposit of an insoluble substance in a solution as a result of a chemical reaction after the addition of a precipitating reagent. Cf. *schoellemeyerite.* **banded ~** Periodic p. **black ~** Mercurous oxide. **group ~** The p. formed by a group precipitant consisting of substances of related properties. See *qualitative analysis* under *analysis.* **periodic ~** See *Liesegang rings.* **red ~** Red *mercuric* oxide. **white ~** Ammoniated *mercury.* **yellow ~** Yellow *mercuric* oxide.

precipitated Settled out; rendered insoluble. **p. bone** A by-product in the manufacture of glue from bones; chiefly calcium hydrogenphosphate. **p. chalk** Calcium carbonate produced by precipitation. **p. phosphate** Calcium hydrogenphosphate obtained from phosphate rock or processed bone. **p. vapor** The deposit of solid particles from gases or vapors on the walls of a container.

precipitation The process of producing a precipitate. **co ~** The simultaneous p. of more than one substance. Cf. *group precipitate.* **electrostatic ~** See *electrostatic precipitator.* **fractional ~** The separation of substances by precipitating them in increasing order of solubility.

precipitin An antibody formed in the serum of animals or humans that precipitates antigens, as, bacteria.

precipitinogen A substance which, on injection, causes the formation of precipitins.

precipitum The deposit formed by the action of precipitins.

precision The degree of mutual agreement between individual measurements, such as the *standard deviation,* q.v., as distinct from their accuracy. **p. instrument** An instrument capable of precise measurements.

precursor (1) A substance synthesized in the dark by an organism, and decomposed by light. Cf. *photoproduct.* (2) A substance that forms the raw material for the synthesis of protoplasm in the living animal body. (3) A substance that precedes the formation of another compound. Cf. *provitamin.*

predissociation A spectral phenomenon by which a molecule dissociates at a lower level than its dissociation energy.

prednisolone $C_{21}H_{28}O_5$ = 360.5. Sterane. Delta Cortef. White, bitter crystals, m.229 (decomp.), soluble in water; a corticone substitute, as it has fewer side effects (USP, EP, BP). **p. sodium phosphate** $C_{21}H_{27}O_8Na_2P$ = 484.4. Bitter, white powder, soluble in water; a synthetic glucocorticoid. Used for its anti-inflammatory effect in blood diseases and allergic states (USP, BP).

prednisone $C_{21}H_{26}O_5$ = 358.4. White, bitter crystals, insoluble in water; used similarly to prednisolone (USP, EP, BP).

preform Material produced in a state ready for molding to a desired shape, e.g., plastic-impregnated wood pulp for molded panels.

Pregl, Fritz (1868–1930) Austrian chemist, noted for his development of quantitative microanalysis. Nobel prize winner (1923).

pregnancy test Detection of chorionic gonadotrophin in urine by antibody-antigen reaction, or by radioimmunoassay of blood serum.

pregnane $C_{21}H_{36}$ = 288.5. A tetracyclic hydrocarbon, androstane derivative. Parent compound of some natural steroids, including mammalian hormones. **p.diol** $C_{21}H_{36}O_2$ = 320.5. A sterol, m.233, from the urine of pregnant women. **p.dione** $C_{21}H_{32}O_2$ = 316.5. A ketone derivative of p. diol. **pregnanolone** $C_{21}H_{34}O_2$ = 318.5. A metabolite of progesterone.

pregnene $C_{21}H_{34}$ = 286.2. $\Delta^{5,6}$-pregnane. An androstane derivative.

pregneninolone Ethisterone.

pregratilie A variety of muscovite from Tyrol.

prehnite $H_2Ca_2Al_2(SiO_4)_3$. A hydrous silicate.

prehnitene C_6H_{14} = 134.2. Prenitol, 1,2,3,4-Tetramethylbenzene*. Colorless liquid, b.204, insoluble in water.

prehnitic acid $C_{10}H_6O_8$ = 254.2. 1,2,3,5-Benzeneteracarboxylic acid*. Colorless crystals, m.252. Cf. *mellophanic acid.*

prehnitilic acid 2,3,4-Trimethylbenzoic acid*.

preignition See *knock.*

preimpregnate (1) To impregnate prior to a subsequent stage in a process. (2) A substance used to hold the ingredients of a mix together, before resin impregnation and molding; e.g., polyester resins.

Prelog, Vladimir (1906–) Bosnian-born Swiss chemist. Nobel prize winner (1975), noted for work on the chirality of organic compounds.

premier alloy A heat-resisting alloy: Ni 61, Fe 25, Cr 11, Mn 3%.

prenyl The 3-methyl-2-butenyl* radical, $Me_2C{:}CH{\cdot}CH_2{-}$.

prep Abbreviation for "preparation."

preparation (1) A chemical process for the production of a